REMARKS

Upon entry of this amendment, Claims 1, 7, and 20 constitute the pending claims in the present application. Solely for the purpose of expediting prosecution, Applicants have amended Claim 1 by partially incorporating the subject matter of former Claim 4. Claims 2-6 are canceled without prejudice. Applicants reserve the right to prosecute claims of identical or similar scope in future continuation or divisional applications.

Applicants note that the IDS received on August 2, 2004 has been considered by the Examiner.

Applicants respectfully request reconsideration in view of the following remarks. Issues raised by the Examiner will be addressed below in the order they appear in the Office Action.

Drawings

The Office Action indicates that certain color drawings (*i.e.*, Figures 1-12) submitted with the instant application are not accepted, because the requirements of 37 C.F.R. § 1.84(a)(2) and (b)(2) have not been met.

Applicants hereby submit a set of black and white drawings for Figures 1-12. Reconsideration and withdrawal of the objection are respectfully requested.

Claim Rejections under 35 U.S.C. § 112, First Paragraph

Claims 1 and 4 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement.

Applicants have amended Claim 1 to expedite prosecution and to clarify the subject matter claimed. Amended Claim 1 recites calcineurin as the NF-AT agonist. Since the Office Action admits that calcineurin is a structurally defined molecule and that the written description requirement is met, reconsideration and withdrawal of the rejection are respectfully requested.

Claims 1 and 4 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Specifically, the Office Action argues that the specification does not enable any skilled artisan to use the invention commensurate in scope with these claims. Applicants respectfully disagree.

Factors to be considered in a determination of lack of enablement includes the eight factors enumerated in *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

Applicants submit that amended Claim 1 recited calcineurin as the NF-AT agonist. Since calcineurin is a defined molecule with known structure, the breadth of the claim is considerably narrower compared to the original Claim 1. Furthermore, the nature of the invention concerns contacting a cell with a polypeptide. At the time of filing the instant application (*e.g.*, April 2004), the level of skill in the art of molecular biology, including in the field of protein expression or delivery is extremely high, as is evidenced partially by the Examples in the instant application (see, for example, Example 12 at page 42).

The Office Action argues that the primary basis of the enablement rejection is the unpredictability of gene therapy in general. The Office Action cites several references cautioning the difficulties in delivering antisense oligonucleotides and siRNA. However, the recited calcineurin is neither antisense RNA or siRNA, thus Applicants' claim amendment renders this rejection moot.

The Office Action further argues that calcineurin mediates a wide range of complex cellular and physiological functions, and treating a subject with calcineurin is expected to cause a variety of responses. However, this argument appears to be concerned with a safety issue, rather than the enablement of the claimed invention. For *in vivo* use, a skilled artisan ought to be able to adjust the level of medicament to be delivered to a particular patient, through no more than routine experimentation, to ensure the safety of a patient. Thus the concern of apoptosis caused by *high level constitutive calcineurin activity* (as indicated in Asai) would not prevent a skilled artisan from practicing the claimed invention.

Finally, the Office Action argues that Applicants have only shown one *in vitro* working example, and have not shown any *in vivo* working examples.

Pursuant to MPEP 2164.02, "[a] rigorous or an invariable exact correlation is not required, as stated in *Cross v. Iizuka*, 753 F.2d 1040, 1050, 224 USPQ 739, 747 (Fed. Cir. 1985): [B]ased upon the relevant evidence as a whole, there is a reasonable correlation between the disclosed *in vitro* utility and an *in vivo* activity, and therefore a rigorous correlation is not necessary where the disclosure of pharmacological activity is reasonable based upon the probative evidence. (Citations omitted.)" Applicants submit that *in vitro* experiments (such as those disclosed in the instant specification) are routinely used by skilled artisan to establish pharmacological activity of medicaments. Thus no rigorous correlation with *in vivo* data is required.

In summary, Applicants submit that all pending claims as amended satisfy the written description and enablement requirements of 35 U.S.C. § 112, first paragraph. Reconsideration and withdrawal of the rejections are respectfully requested.

Claim Rejections under 35 U.S.C. § 102

The Office Action states that Claims 1 and 4 are rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Graef (*Nature* **401**: 703-708, 1999). The Office Action argues that Graef shows a method for activating endogenous NF-AT in cultured hippocampal neurons comprising transfecting the neurons with constitutively active calcineurin (Figure 1c and page 703), or treating the neurons with ionomycin (Figure 1d and page 703).

Applicants submit that amended method Claim 1 is not anticipated by Graef, which teaches activation of calcineurin in hippocampal neurons to *induce synaptic plasticity and memory formation*, rather than *promoting axonal growth*, as is recited in the claimed invention. This is analogous to a situation where a drug (such as ASPIRIN) can be used for multiple diverse treatment methods (such as treating stroke, heart attack, Rheumatologic and other inflammatory diseases, pain relief, or reducing the risk of colon cancer, *etc.*), each treatment method does not necessarily anticipate the other treatment methods, despite the fact that the different treatment methods all comprise essentially the same method step – administering the drug to the patient.

Therefore, Graef does not anticipate the amended claims. Reconsideration and withdrawal of the rejection under 35 U.S.C. § 102(b) are respectfully requested.

The Office Action also states that Claim 1 is rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Serafini (*Cell* **78**: 409-424, 1994).

Since the amended Claim 1 corresponds to former Claim 4 in scope, Serafini does not anticipate the amended Claim 1. Reconsideration and withdrawal of the rejection under 35 U.S.C. § 102(b) are respectfully requested.

The Office Action also states that Claim 1 is rejected under 35 U.S.C. § 102(e) as allegedly being anticipated by Butler (US 2003/0211608).

Since the amended Claim 1 corresponds to former Claim 4 in scope, Butler does not anticipate the amended Claim 1. Reconsideration and withdrawal of the rejection under 35 U.S.C. § 102(b) are respectfully requested.

CONCLUSION

For the foregoing reasons, Applicants respectfully request reconsideration and withdrawal of the pending rejections. Applicants believe that the claims are now in condition for allowance and early notification to this effect is earnestly solicited. Any questions arising from this submission may be directed to the undersigned at (617) 951-7000.

If there are any other fees due in connection with the filing of this submission, please charge the fees to our **Deposit Account No. 18-1945,** under Order No. **SUPP-P01-007**.

Dated: November 1, 2006

Respectfully submitted,

By_____

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